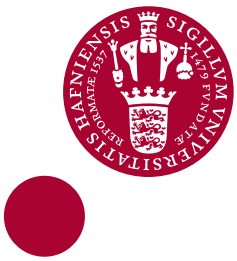

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Phase II randomised clinical trial

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The effect of remote ischaemic preconditioning on myocardial injury in emergency hip fracture surgery (PIXIE trial): phase II randomised clinical trial

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ABSTRACT

OBJECTIVE

To investigate whether remote ischaemic preconditioning (RIPC) prevents myocardial injury in patients undergoing hip fracture surgery.

DESIGN

Phase II, multicentre, randomised, observer blinded, clinical trial.

SETTING

Three Danish university hospitals, 2015-17.

PARTICIPANTS

648 patients with cardiovascular risk factors undergoing hip fracture surgery. 286 patients were assigned to RIPC and 287 were assigned to standard practice (control group).

INTERVENTION

The RIPC procedure was initiated before surgery with a tourniquet applied to the upper arm and consisted of four cycles of forearm ischaemia for five minutes followed by reperfusion for five minutes.

MAIN OUTCOME MEASURES

The original primary outcome was myocardial injury within four days of surgery, defined as a peak plasma cardiac troponin I concentration of 45 ng/L or more caused by ischaemia. The revised primary outcome was myocardial injury within four days of surgery, defined as a peak plasma cardiac troponin I concentration of 45 ng/L or more or high sensitive troponin I greater than 24 ng/L (the primary outcome was changed owing to availability of testing). Secondary outcomes were peak plasma troponin I and total troponin I release during the first four days after surgery (cardiac and high sensitive troponin I), perioperative myocardial infarction, major adverse cardiovascular events, and all cause mortality within 30 days of surgery, length of postoperative stay, and length of stay in the intensive care unit. Several planned secondary outcomes will be reported elsewhere.

RESULTS

573 of the 648 randomised patients were included in the intention-to-treat analysis (mean age 79 (SD 10) years; 399 (70%) women). The primary outcome occurred in 25 of 168 (15%) patients in the RIPC group and 45 of 158 (28%) in the control group (odds ratio 0.44, 95% confidence interval 0.25 to 0.76; P=0.003). The revised primary outcome occurred in 57 of 286 patients (20%) in the RIPC group and 90 of 287 (31%) in the control group (0.55, 0.37 to 0.80; P=0.002). Myocardial infarction occurred in 10 patients (3%) in the RIPC group and 21 patients (7%) in the control group (0.46, 0.21 to 0.99; P=0.04). Statistical power was insufficient to draw firm conclusions on differences between groups for the other clinical secondary outcomes (major adverse cardiovascular events, 30 day all cause mortality, length of postoperative stay, and length of stay in the intensive care unit).

CONCLUSIONS

RIPC reduced the risk of myocardial injury and infarction after emergency hip fracture surgery. It cannot be concluded that RIPC overall prevents major adverse cardiovascular events after surgery. The findings support larger scale clinical trials to assess longer term clinical outcomes and mortality.

TRIAL REGISTRATION

ClinicalTrials.gov NCT02344797.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Cardiovascular morbidity is common after non-cardiac surgery, with myocardial injury the most prominent outcome

Remote ischaemic preconditioning (RIPC) is an inexpensive intervention that could prevent myocardial injury without substantial adverse effects although no randomised trial has examined its effect versus standard treatment in non-cardiac surgery

Myocardial injury is associated with myocardial infarction and short and long term mortality, but could be emerging as a separate clinical relevant outcome although it is not yet clear how myocardial injury should be managed

WHAT THIS STUDY ADDS

RIPC reduced myocardial injury after non-cardiac surgery as well as myocardial infarction (the only sufficiently powered secondary outcome); the magnitude of this reduction is still uncertain

Further trials including those large enough to reliably measure more established cardiovascular diagnoses are needed

This study does not support change in practice

Introduction

Worldwide, more than 200 million people undergo major non-cardiac surgery annually.[1] The average overall complication rate is 7% to 11% and the 30 day mortality is around 0.8% to 1.5%.[2 3] At a minimum, one third of the postoperative deaths are caused by cardiovascular complications.[2] In general, mortality due to cardiac diseases is decreasing, which consequently results in an elderly population with a greater number of cardiac comorbidities, including ischaemic heart disease, heart failure, and

cardiovascular risk factors.[2] In Europe alone, the number of patients undergoing surgery in general will increase by 25% by 2020 and the elderly population will increase by almost 50%.[2] In the years to come, managing elderly surgical patients with multiple cardiovascular comorbidities will be a frequent challenge in perioperative medicine.

Myocardial injury in non-cardiac surgery (MINS), defined as myocardial injury caused by ischaemia, has prognostic relevance and occurs during or within 30 days after non-cardiac surgery.[4] Several clinical studies have shown MINS to be associated with a 2-3-fold increased risk of subsequent major adverse cardiovascular events and postoperative mortality.[4-7] Thus MINS is recognised as a surrogate for myocardial infarction after non-cardiac surgery because patients often do not experience ischaemic symptoms after surgery.[8] In 2018, MINS was established as a diagnosis in the fourth universal definition of myocardial infarction (European Society of Cardiology clinical practice guidelines).[9] As MINS is now recognised by the European Society of Cardiology,[9] it could be emerging as a potential diagnosis in its own right. To date no intervention has resulted in a reduction in MINS and it is a condition that has no agreed treatment.

The well known procedure of remote ischaemic preconditioning (RIPC) might protect remote tissues and organs from, for example, reperfusion injury.[10] Cycles of forearm ischaemia and reperfusion by the inflation of a blood pressure cuff for brief periods is the preferred method. The procedure is simple and safe and has no known adverse effects in patients undergoing elective cardiovascular surgery and in those with ST elevation myocardial infarction.[10] The mechanism of RIPC is not fully understood. Experimental and clinical studies have suggested that the local tissue injury caused by RIPC might activate humoral mediators (eg, adenosine, bradykinin, antioxidants) and initiate a neuronal signal transfer leading to a cytoprotective state but also activation of systemic anti-inflammatory and antithrombotic mechanisms and endothelial protection.[11-14] Surgery is known to activate a severe stress response resulting in, for instance, immunological dysfunction, hypercoagulability, endothelial dysfunction, and activation of the sympathetic nervous system, all of which are likely to contribute to the pathophysiology of MINS and perioperative cardiovascular events.[15-17] The detrimental systemic effects of surgery therefore might potentially be reduced by RIPC.

We carried out a randomised clinical trial (Prevention of Myocardial Injury by Remote Ischaemic Preconditioning in Non-cardiac Surgery, PIXIE) to test the hypothesis that RIPC compared with standard treatment reduces the incidence of myocardial injury (primary outcome) after hip fracture surgery.

Methods

Trial design

The PIXIE trial was a phase II proof of concept, multicentre, randomised, observer blinded, clinical trial. All patients received oral and written information about the trial and signed an informed consent form before inclusion. The trial was reported according to the CONSORT statement[18] and registered on ClinicalTrials.gov.

Changes were made to the methods after trial commencement. The original primary outcome was revised in October 2015 after the start of the trial in February 2015. The original primary outcome was based on an increase in cardiac troponin I level, whereas the revised primary outcome was based on an increase in cardiac troponin I or high sensitive troponin I level. We modified the outcome because a new trial site, Regional Hospital West Jutland, was included. This site exclusively assessed high sensitive troponin I. The decision to include this trial site was independent of the data we had already obtained.

In October 2015 we modified the secondary outcomes peak cardiac troponin I and total cardiac troponin I release to peak troponin I and total troponin I release stratified on cardiac troponin I and high sensitive troponin I. This was because of the assessment of high sensitive troponin I at Regional Hospital West Jutland.

The trial was initially designed to include patients undergoing major emergency abdominal or hip fracture surgery. As the recruitment of patients undergoing abdominal surgery was challenging in October 2015 we decided to exclusively include patients undergoing hip fracture surgery. The abdominal surgical patients already included in the trial were not included in the final analysis.

A criterion was added to exclude patients with a new fracture of the upper arm, after a small group of such patients was identified during screening.

Reporting

The secondary outcomes concerning plasma NT-pro BNP (N-terminal prohormone B type natriuretic peptide) and the analyses of a subgroup of patients with endothelial dysfunction and biomarkers of coagulation are not reported here. We have planned to report separately the details of potential mechanisms behind the effect of RIPC. Moreover, the long term clinical effect of RIPC in the whole cohort will be published once data is available. We presented major adverse cardiovascular events as a composite outcome (as registered in the protocol and on ClinicalTrials.gov) and the separate clinical outcomes. We believe that the presentation of the separate clinical outcomes is informative.

Participants

We included adults aged 45 years or older undergoing hip fracture surgery and with a minimum of one of four risk factors: ischaemic heart disease, defined as angina pectoris, prior myocardial infarction, prior percutaneous coronary intervention or prior coronary artery bypass grafting; peripheral arterial disease, defined as intermittent claudication, reduced peripheral arterial blood flow or previous vascular surgery due to peripheral arterial disease; previous

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stroke; and any one of seven cardiovascular risk factors (age ≥70 years, congestive heart failure, previous transient ischaemic attack, diabetes and currently taking an oral hypoglycaemic agent or insulin, hypertension, preoperative serum creatinine concentration >175 µmol/L, smoking within two years of surgery). Exclusion criteria were a history of peripheral arterial disease affecting both arms, renal failure (estimated glomerular filtration rate <30 mL/min/1.73m^2), cardiogenic shock or cardiac arrest during the current hospital stay (before inclusion), another operation during the current hospital stay (before inclusion), experience of a condition that prevented the performance of RIPC, not capable of giving informed consent, and previously enrolled in the trial. We did not exclude patients who were being treated with drugs such as β blockers, dabigatran, sulphonamide, or nicorandil. Nor did we exclude patients with recent myocardial infarctions or chronic ischaemia. Patients were recruited from three Danish hospitals, all secondary referral centres, and data were collected at the hospitals.

Trial randomisation and blinding

Patients were randomly allocated to RIPC or control. A third party (a research fellow) generated the random allocation sequence using an electronic randomisation plan generator (www.randomization.com). The allocation ratio was 1:1 in fixed blocks of six. The nurse anaesthetist opened a sealed opaque envelope in the operating theatre and allocated the patient accordingly. Owing to the nature of the intervention, it was not possible to blind the anaesthetist, nurse anaesthetist, surgeon (treating clinician), surgical staff, and local investigators caring for the patient. The cardiologists taking part in the clinical treatment were, however, blinded. The principal investigator (SE), who determined whether an increase in troponin level was ischaemic or non-ischaemic based, was blinded to the intervention. Patients receiving regional anaesthesia without sedation were not blinded to the allocated treatment, whereas patients receiving general anaesthesia were blinded to the allocated treatment.

Trial intervention

Patients in the control group received standard care before, during, and after surgery according to local guidelines. Patients in the intervention group received the same standard of care along with the RIPC procedure. The management did not differ in any other way between the two trial groups. The RIPC procedure was performed with a tourniquet applied to the upper arm and consisted of four cycles of forearm ischaemia and reperfusion. The RIPC procedure was performed with an electric tourniquet device (Tourniquet 4500 ECL; VBM Medizintechnik, Sulz am Neckar, Germany). The tourniquet was inflated to 200 mm Hg for five minutes followed by deflation and five minutes of reperfusion. The procedure took 40 minutes. For patients with a systolic blood pressure greater than 185 mm Hg, the tourniquet was inflated to a minimum of 15 mm Hg above the patient's systolic blood pressure. The nurse anaesthetist performed the RIPC in the operating theatre after induction of general or regional anaesthesia. The first round of ischaemia and reperfusion was completed before skin incision, whereas the remaining rounds could be performed during surgery. The intervention was considered complete when all four cycles had been administered. To standardise the RIPC, the investigators instructed the nurse anaesthetists on how to perform the procedure. The exact time of each cycle, technical difficulties, and disruptions were noted. The choice of anaesthesia and analgesia was left to the treating anaesthesiologist. Perioperative and postoperative care followed the departments' standard protocol.

Trial outcomes

Troponin I was collected soon before surgery and in the morning on postoperative days 1 (the morning of the first postoperative day) to 4. An increase in troponin I was defined as a cardiac troponin I concentration of 45 ng/L or more or high sensitive troponin I concentration greater than 24 ng/L. If the levels were raised, a minimum of one electrocardiographic procedure was performed irrespective of symptoms and the patient was evaluated for the presence of an ischaemic or non-ischaemic event to explain the increased troponin I. A cardiologist was consulted if necessary. Research staff collected data prospectively, and follow-up at 30 days was carried out by review of the electronic medical records in each of the hospitals. The Danish electronic medical records are automatically updated on vital status within days of death.

Primary outcomes

The prespecified primary outcome as stated in the original registration and protocol was MINS within four days of hip fracture surgery. MINS is a surrogate for myocardial infarction after non-cardiac surgery but might be emerging as a separate clinical relevant outcome.[9 19] The original primary outcome, MINS, was defined as a peak plasma cardiac troponin I concentration of 45 ng/L or more, whereas the revised primary outcome was defined as a peak plasma cardiac troponin I concentration of 45 ng/L or more or high sensitive troponin I greater than 24 ng/L. The blinded primary investigator (SE) excluded non-ischaemic causes of raised troponin levels—for example, sepsis, pulmonary embolus, rapid atrial fibrillation, chronic raised troponin level. Patients had to have a minimum of two postoperative troponin assessments within four days of surgery. If levels were raised above the limits before surgery (baseline), an increase of minimum 20% from the baseline troponin I level was required for the diagnosis of MINS.

Two hospitals (Zealand University Hospital and Herlev Hospital) assessed cardiac troponin I using the Healthcare Dimension Vista assay (Siemens, Munich, Germany) with a cut-off of 45 ng/L or more (99th centile upper reference limit, 10% coefficient of variation at 40 ng/L), and one hospital (Regional Hospital West

Jutland) assessed high sensitive troponin I using an Abbott assay (Abbott, IL) with a cut-off greater than 24 ng/L (99th centile upper reference limit, 14% coefficient of variation).

Secondary outcomes

Several secondary outcome measures were included. (1) peak plasma troponin I and total troponin I release (area under the curve) during surgery or during the first four days after surgery stratified on cardiac troponin I and high sensitive troponin I. (2) Perioperative myocardial infarction (universal definition of myocardial infarction, published in 2012[20]) defined by (A) a typical increase or decrease in cardiac troponin I level with peak plasma cardiac troponin I of 45 ng/L or more (99th centile upper reference limit, 10% coefficient of variation at 40 ng/L) (Regional Hospital West Jutland high sensitive troponin I >24 ng/L), and with at least one of the following: symptoms of ischaemia, new or presumed new ST segment T wave changes or new left bundle branch block, development of ischaemic Q waves in the electrocardiogram, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy. (B) Cardiac related death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic electrocardiographic changes or new left bundle branch block, but death occurred before cardiac biomarkers were obtained or before cardiac biomarker values would be increased. (C) Development of new ischaemia related Q waves on an electrocardiogram or other electrocardiographic findings of a healing myocardial infarction if troponin levels were obtained at times that could have missed the clinical event. (3) Major adverse cardiovascular events within 30 days of surgery defined as non-fatal cardiac arrest, coronary revascularisation procedure (percutaneous coronary intervention or coronary artery bypass graft), acute coronary syndrome, stroke, congestive heart failure, new clinically important cardiac arrhythmia, peripheral arterial thrombosis, or readmission to hospital for cardiovascular reasons. (4) Length of postoperative hospital stay. (5) Length of stay on an intensive care unit. (6) All cause mortality at 30 days (cardiovascular or non-cardiovascular cause, with the latter clearly documented).

The primary investigator (SE) blinded to the treatment allocation determined whether an increase in troponin level was ischaemic related (the lack of a non-ischaemic event) or non-ischaemic related, and whether a death was related to a cardiovascular or non-cardiovascular cause. During the hospital admission, patients were observed for local adverse effects of RIPC, including pain in the upper arm, sensory disturbances, and local skin irritation.

Sample size

In a large cohort study performed by the VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation) investigator group, 8.0% of the patients undergoing non-cardiac surgery experienced MINS.[4] In our trial, PIXIE, we included patients with a moderate to high risk of MINS, whereas the VISION study[4] included patients at all risk levels. We assumed that 15% of the patients in the control group would experience MINS and assumed that RIPC would reduce the event rate of MINS to 7%. With a risk of a type I error of 5% and a type II error of 20%, we calculated that 264 patients in each group would provide adequate power to detect a difference of 8%.

Statistical analysis

All patients with an evaluable primary outcome, MINS within four days of surgery, were included in the intention-to-treat analysis regardless of whether they received the allocated treatment. The intention-to-treat analysis was the primary analysis of the PIXIE trial. Patients included in the per protocol analysis received the allocated treatment and had an evaluable primary outcome.

We used the χ^2 test to compare the event rates of MINS, major adverse cardiovascular events and the individual cardiovascular events, and all cause mortality. Troponin I release from baseline to day 4 after surgery was calculated separately for the two different troponin I assays by the means of area under the curve. Peak troponin I, area under the curve troponin I, and length of stay in the intensive care unit were expressed as median (interquartile range) and analysed with a Wilcoxon two sample test. Length of stay was expressed as mean (95% confidence interval) and compared with an unpaired t test. Moreover, we compared the event rate of increased troponin I levels, ischaemic and non-ischaemic, in both treatment groups with the χ^2 test. Univariable and multivariable logistic regressions were used to analyse the association between the intervention and MINS (revised primary outcome). The multivariable analysis was adjusted for predefined variables, including age group, sex, ischaemic heart disease, stroke, congestive heart failure, peripheral arterial disease, diabetes, acetylsalicylic acid, type of anaesthesia, number of measurements for troponin I, and trial site. We tested potential predefined interactions between age group and sex, intervention and type of anaesthesia, and intervention and trial site. None were statistically significant ($P<0.05$) and therefore not included in the final analysis. To avoid overfitting of the model we included a maximum of one variable for every 10 events in the multivariable logistic regression. The goodness of fit for the multivariable logistic regression was tested with a Hosmer and Lemeshow test.

We performed two post hoc subgroup analyses. We analysed the effect of RIPC on MINS in patients who received or did not receive propofol for sedation, induction, or maintenance of anaesthesia. Moreover, we analysed the effect of RIPC in patients undergoing general anaesthesia compared with regional anaesthesia. Statistical analyses were performed in SAS version 9.4 (SAS Institute) and graphics were created

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in GraphPad Prism version 6. We considered a two sided P value <0.05 to be significant.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advice on interpretation or writing up the results. All participants will be informed of the trial results by mail. The trial results will be disseminated to the public through online science media.

Results

Patient flow and baseline characteristics

Recruitment took place between February 2015 and September 2017. The last follow-up was in October 2017. Figure 1 shows the flow of participants through the trial. Among 648 randomised patients, 573 patients were included in the intention-to-treat analysis (Zealand University Hospital n=281, Herlev Hospital n=45, Regional Hospital West Jutland n=247) and 559 patients in the per protocol analysis.

Table 1 shows the characteristics of the study population. Most of the patients were women, with a mean age of 78.8 (SD 10.1) years in the RIPC group and 79.2 (9.8) years in the control group. In both groups, hypertension and hypercholesterolaemia were the most common cardiovascular comorbidities, and 15% (43/286) of patients in the RIPC group and 15% (42/287) in the control group had a history of ischaemic heart disease. The groups were similar for preoperative drug treatment except for acetylsalicylic acid, which was more commonly used in the RIPC group compared with control group (25% (71/286) *v* 17% (48/287); P=0.02). Perioperative characteristics were similar between the groups (table 2).

None of the patients experienced any local adverse effects of RIPC. Eight out of 316 patients allocated to RIPC (2%) did not complete the procedure owing to discomfort and nine out of 316 patients (3%) did not complete the procedure owing to technical difficulties (fig 1).

Primary outcomes

The original primary outcome occurred in 25 out of 168 patients (15%) in the RIPC group and 45 out of 158 (28%) in the control group (odds ratio 0.44, 95% confidence interval 0.25 to 0.76; P=0.003). The revised primary outcome occurred in 57 out of 286 patients (20%) in the RIPC group and in 90 out of 287 (31%) in the control group (0.55, 0.37 to 0.80; P=0.002). When including both ischaemic and non-ischaemic increases in troponin levels, 69 out of 286 patients (24%) had raised troponin levels in the RIPC group and 103 out of 287 (36%) in the control group,

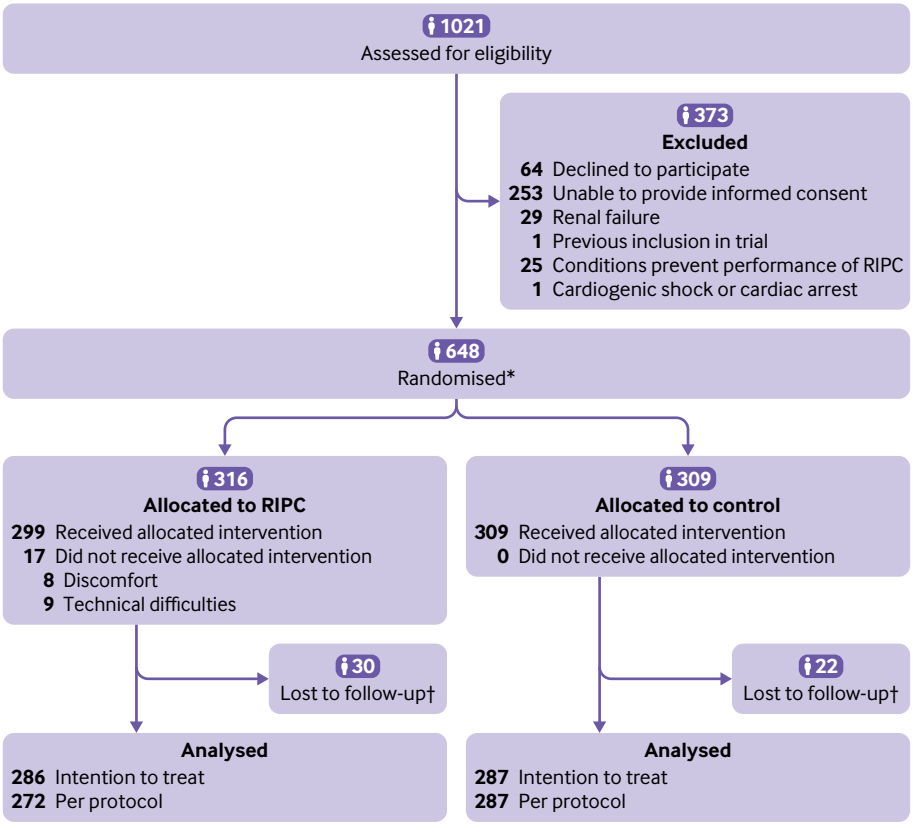

Fig 1 | Flow of participants through study. *Includes 23 patients undergoing emergency abdominal surgery (patients were excluded from analyses and final part of flow chart). †No evaluable primary outcome. RIPC=remote ischaemic preconditioning

Table 1 | Baseline characteristics of patients assigned to remote ischaemic preconditioning (RIPC) or standard practice (control). Values are numbers (percentages) unless stated otherwise

Characteristics	RIPC group (n=286)	Control group (n=287)
Mean (SD) age (years)	78.8 (10.1)	79.2 (9.8)
Women	199 (70)	200 (70)
Mean (SD) body mass index	23.4 (4.2)	23.9 (4.3)
Smoker:		
No	124 (43)	118 (41)
Current	93 (32)	76 (26)
Former	69 (24)	93 (32)
Alcohol consumption*:		
None	58 (20)	58 (20)
<limit	188 (66)	185 (64)
>limit	40 (14)	44 (15)
Mean (SD) preoperative blood pressure (mm Hg):		
Systolic	145.4 (24.9)	146.8 (22.6)
Diastolic	75.8 (14.9)	76.5 (14.2)
ASA score†:		
I-II	164 (57)	167 (58)
III-IV	122 (43)	120 (42)
Revised cardiac risk index‡:		
I-II	256 (89)	255 (89)
III-IV	30 (10)	32 (11)
Median (interquartile range) preoperative troponin I level (ng/L):		
Cardiac	15.0 (15.0-30.0)	15.0 (15.0-34.5)
High sensitive	10.0 (10.0-23.0)	10.5 (10.0-25.0)
Mean (SD) No of postoperative troponin I measurements:		
2	40 (14.0)	28 (9.8)
3	67 (23.4)	65 (22.6)
4	179 (62.6)	194 (67.6)
Mean (SD) timing of troponin I measurements (hours after surgery):		
1	19.5 (4.7)	19.4 (4.4)
2	43.3 (4.4)	43.1 (4.5)
3	67.2 (4.6)	67.0 (4.8)
4	91.1 (5.0)	90.8 (5.6)
Mean (SD) preoperative haemoglobin (g/L)	126.9 (15.5)	127.9 (16.6)
Median (interquartile range) creatinine (mg/dL):		
Preoperative	0.75 (0.60-0.98)	0.80 (0.63-1.03)
Postoperative:		
Day 1	0.75 (0.59-0.92)	0.75 (0.62-0.96)
Day 2	0.72 (0.58-0.95)	0.64 (0.71-1.01)
Day 3	0.70 (0.57-0.90)	0.75 (0.58-0.95)
Day 4	0.69 (0.58-0.89)	0.73 (0.57-0.94)
Median (interquartile range) eGFR (mL/min/1.73m^2):		
Preoperative	81.0 (60.0-90.0)	78.0 (57.0-90.0)
Postoperative:		
Day 1	80.0 (63.0-90.0)	80.0 (60.0-90.0)
Day 2	82.0 (63.0-90.0)	80.0 (58.0-90.0)
Day 3	85.0 (67.0-90.0)	82.0 (63.0-90.0)
Day 4	84.5 (66.0-90.0)	81.5 (62.0-90.0)
Comorbidities:		
Ischaemic heart disease	43 (15)	42 (15)
Peripheral arterial disease	18 (6)	19 (7)
Stroke	44 (15)	44 (15)
Congestive heart failure	26 (9)	25 (9)
Transient cerebral ischaemia	18 (6)	11 (4)
Diabetes	39 (14)	37 (13)
Hypertension	176 (61)	195 (68)
Hypercholesterolaemia	90 (31)	89 (31)
Chronic kidney disease	14 (5)	8 (3)
Atrial fibrillation	62 (22)	54 (19)
Chronic obstructive pulmonary disease	57 (20)	56 (19)
Cancer	18 (6)	21 (7)
Preoperative drugs:		
Acetylsalicylic acid§	71 (25)	48 (17)
Platelet inhibitors	27 (9)	26 (9)
Vitamin K antagonist	29 (10)	31 (11)
DOAC	17 (6)	21 (7)
β blocker	69 (24)	78 (27)

Table 1 | Continued

Characteristics	RIPC group (n=286)	Control group (n=287)
Calcium antagonist	70 (24)	81 (28)
ACE inhibitor or ARB	113 (39)	123 (43)
Diuretics	108 (38)	118 (41)
Statin	89 (31)	89 (31)
Isosorbide mononitrate	15 (5)	8 (3)
Antidiabetics	24 (8)	21 (7)
Insulin	20 (7)	19 (7)

ACE=angiotensin-converting enzyme; ASA=American Society of Anesthesiologists; ARB=angiotensin II receptor blocker; DOAC=direct oral anticoagulant; eGFR=estimated glomerular filtration rate.
*≤7 units/week for women and ≤14 units/week for men.
†Score of physical health. I-II: good physical health. III-IV: poor physical health.
‡Score of postoperative risk of cardiac complications. I-II: low risk. III-IV: high risk.
§P=0.02.

P=0.002. Supplementary table 1 lists the causes of non-ischaemic increases in troponin levels. The timing and number of measurements for troponin I did not differ between the groups (table 1, supplementary table 2). In the RIPC group, an unadjusted subgroup analysis showed that the incidence of MINS was significantly reduced in the group that received propofol compared with the group that did not receive propofol (40/231 patients (17%) *v* 17/55 patients (31%); odds ratio 0.47, 95% confidence interval 0.24 to 0.91; P=0.03). No difference was found when the effect of RIPC on preventing MINS was analysed in patients receiving general anaesthesia compared with regional anaesthesia (29/142 patients (20%) *v* 28/144 patients (19%), 0.94, 0.53 to 1.7; P=0.84).

Secondary outcomes

Peak troponin I and total troponin I release stratified on cardiac troponin I and high sensitive troponin I were statistically similar in the intervention groups (table 3). In the RIPC group, 3% (10/286) of patients experienced a perioperative myocardial infarction within 30 days of surgery compared with 7% (21/287) in the control group (odds ratio 0.46, 95% confidence interval 0.21 to 0.99; P=0.04). No statistically significant difference was found between the groups for major adverse cardiovascular events within 30 days of surgery, hospital length of stay, length of stay in the intensive care unit, or 30 day all cause mortality (table 3). The per protocol analyses showed similar results (supplementary tables 3 and 4). A multivariable logistic regression analysis adjusted for sex, age group, use of acetylsalicylic acid, number of postoperative troponin I measurements, type of anaesthesia, study site, pre-existing congestive heart failure, former stroke, pre-existing ischaemic heart disease, pre-existing peripheral vascular disease, and pre-existing diabetes mellitus showed a significant association between the intervention with RIPC and a reduced risk of MINS (adjusted odds ratio 0.54, 95% confidence interval 0.35 to 0.81; P=0.003). Figure 2 shows the results of the multivariable analysis (see supplementary table 5 for the results of the univariable and multivariable logistic regressions). The multivariable logistic regression showed no interaction between age group and sex (P=0.39), intervention and type of anaesthesia (P=0.24), and intervention and trial site (P=0.21).

Table 2 | Perioperative characteristics of patients assigned to remote ischaemic preconditioning (RIPC) or standard practice (control). Values are numbers (percentages) unless stated otherwise

Characteristics	RIPC group (n=286)	Control group (n=287)
Surgical procedure:		
Internal fixation	130 (45)	116 (40)
Intramedullary rod	57 (20)	76 (26)
Hemi hip replacement	51 (18)	42 (15)
Total hip replacement	48 (17)	53 (18)
Median (interquartile range) duration of surgery (mins)	57.0 (40.0-74.0)	60.0 (45.0-82.0)
Anaesthesia:		
Epidural	103 (36)	83 (29)
Spinal	41 (14)	58 (20)
Total intravenous	36 (13)	37 (13)
Inhalational	106 (37)	109 (38)
Propofol use:		
General anaesthesia induction	95 (33)	97 (34)
General anaesthesia induction and maintenance	36 (13)	37 (13)
Sedation	100 (35)	92 (32)
Median (interquartile range) propofol dose (mg)	120.0 (80.0-207.5)	111.0 (72.7-230.0)
Median (interquartile range) blood loss (mL)	150.0 (50.0-250.0)	150.0 (50.0-300.0)
Transfusion	14 (5)	15 (5)
Median (interquartile range) transfusion volume (mL)	400.0 (300.0-600.0)	300.0 (284.3-600.0)
Median (interquartile range) systolic blood pressure <100 mm Hg (mins)	35.0 (22.0-60.0)	44.5 (22.0-70.0)

Table 3 | Primary and secondary outcomes in patients assigned to remote ischaemic preconditioning (RIPC) or standard practice (control). Values are numbers (percentages) unless stated otherwise

Outcomes	RIPC group (n=286)	Control group (n=287)	Odds ratio (95% CI)	P value
MINS:				
Original primary outcome (n=326)	25/168 (15)	45/158 (28)	0.44 (0.25 to 0.76)	0.003
Revised primary outcome (n=573)	57/286 (20)	90/287 (31)	0.55 (0.37 to 0.80)	0.002
Peak troponin I level (ng/L):				
Median (interquartile range) cardiac troponin I (n=326)	22.0 (15.0-49.50)	27.5 (15.0-102.0)		0.27
Median (interquartile range) high sensitive troponin I (n=247)	17.0 (10.0-43.0)	24.0 (10.0-54.0)		0.17
Area under curve (ng/L/h):				
Median (interquartile range) cardiac troponin I (n=326)	1518.0 (1380.0-2928.0)	1776.0 (1380.0-4632.0)		0.09
Median (interquartile range) high sensitive troponin I (n=247)	996.0 (960.0-2436.0)	1224.0 (960.0-3540.0)		0.12
MACE*	27 (9)	36 (12)	0.73 (0.43 to 1.23)	0.24
Myocardial infarction	10 (3)	21 (7)	0.46 (0.21 to 0.99)	0.04
Stroke	3 (1)	6 (2)	0.50 (0.12 to 2.00)	0.50
Congestive heart failure	3 (1)	5 (2)	0.60 (0.14 to 2.53)	0.72
Peripheral arterial disease	0 (0)	1 (0.3)		1.00
Percutaneous coronary intervention	0 (0)	3 (1)		0.25
CABG	0 (0)	0 (0)		1.00
Clinically important arrhythmia	15 (5)	11 (4)	1.39 (0.63 to 3.08)	0.42
Non-fatal cardiac arrest	1 (0.3)	2 (1)	0.50 (0.045 to 5.55)	0.37
Cardiovascular mortality	2 (1)	4 (1)	0.50 (0.09 to 2.74)	0.69
Cardiovascular hospital readmission	3 (1)	2 (1)	1.51 (0.25 to 9.11)	0.69
Mean (95% CI) length of stay (days)	7.1 (6.7 to 7.5)	7.2 (5.0 to 7.7)	-	0.74
Median (interquartile range) length of stay in ICU (days)	1.0 (0.5-5.5)	1.0 (0.5-2.0)	-	1.00
30 day all cause mortality	5 (2)	9 (3)	0.55 (0.18 to 1.66)	0.29

MINS=Myocardial injury in non-cardiac surgery; MACE=major adverse cardiovascular events; CABG=coronary artery bypass grafting; ICU=intensive care unit.
*Myocardial infarction, non-fatal cardiac arrest, stroke, primary percutaneous coronary intervention, coronary artery bypass grafting, cardiovascular readmission to hospital, peripheral arterial disease, congestive heart failure, clinically important arrhythmia, and cardiovascular mortality.

Discussion

In this phase II multicentre, randomised, observer blinded, clinical trial including 573 patients undergoing hip fracture surgery, remote ischaemic preconditioning (RIPC) reduced the incidence of myocardial injury from 28% to 15% (odds ratio 0.44, 95% confidence interval 0.25 to 0.76) and myocardial infarction within 30 days of surgery from 7% to 3% (0.46, 0.21 to 0.99). In recent years, several preventive strategies have been examined to reduce the risk of myocardial infarction and major adverse cardiovascular events in non-cardiac surgery.[21-23] In this trial we show an effective, simple, and clinically applicable perioperative method to reduce the risk of myocardial injury.

Comparison with other studies

RIPC has been known since the 1990s when a study found that brief episodes of ischaemia to one part of canine myocardium protected remote myocardium from ischaemia and reperfusion injury.[24] Since then several randomised clinical trials have reported an effect of RIPC on reducing myocardial reperfusion injury and major adverse cardiovascular events in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention.[25-28] Recent studies investigating the effect of RIPC in patients undergoing cardiac surgery did not find any effect of RIPC on the clinical outcomes, including myocardial infarction and postoperative mortality, despite phase II randomised clinical trials finding a reduced overall postoperative troponin-T release in the RIPC group.[29-31]

Strengths and limitations of this study

At the study sites, assessments of troponin I were usual clinical practice. In the literature, the definition of myocardial injury in non-cardiac surgery (MINS) is based on troponin T.[32 33] In our trial, we chose to define the MINS threshold as the 99th centile of the upper reference limit for each of the troponin I assays. This approach is in accordance with the clinical practice guidelines by the European Society of Cardiology.[9] The threshold could potentially be too low to have prognostic importance and MINS might be overestimated in both groups. MINS defined by high sensitive troponin I level was slightly more sensitive than MINS defined by cardiac troponin I level, which could explain the high rate of MINS in our study, but the multivariable regression analysis showed no statistically significant difference between the trial sites. A Scandinavian study examined the incidence of a raised troponin T level as a sign of MINS in patients undergoing hip fracture surgery.[5] The diagnosis of MINS was based on the fourth generation troponin T threshold. The study reported that 31% of the patients experienced MINS within two days of surgery, which is similar to the incidence of MINS in our control group.[5] Patients with hip fractures are at

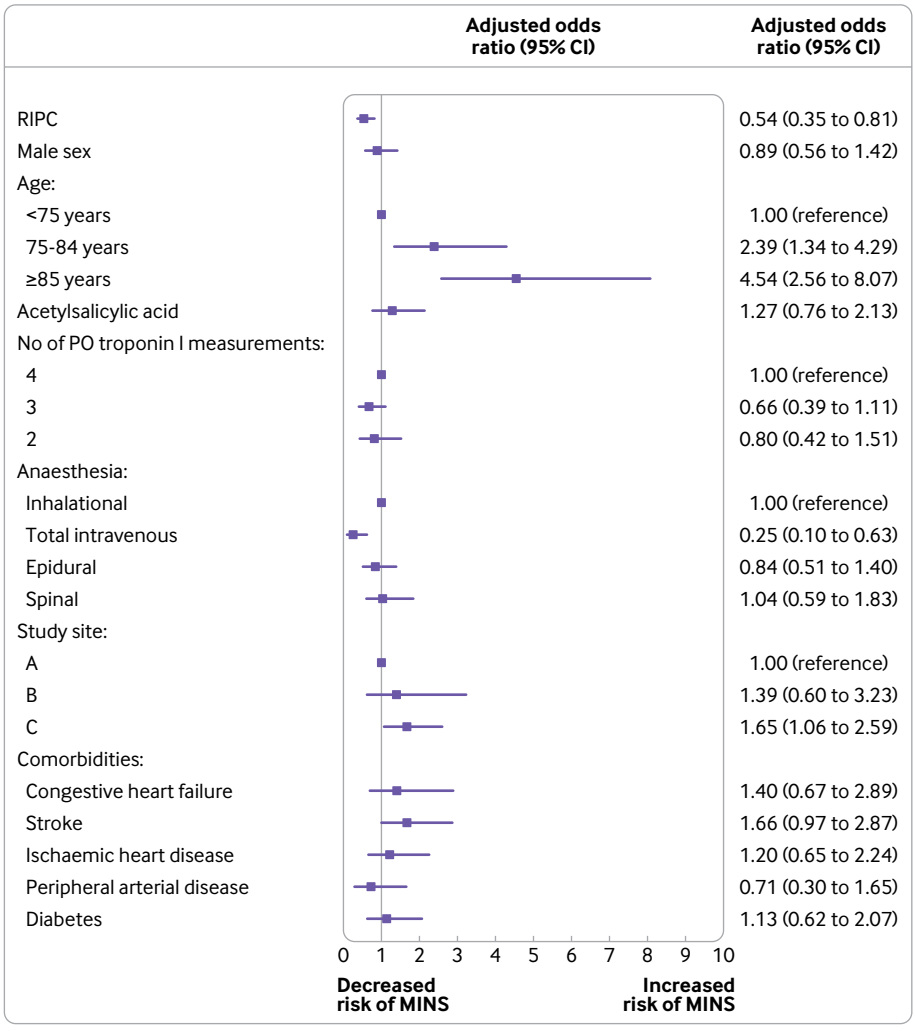

Fig 2 | Forest plot of multivariable logistic regression. RIPC=remote ischaemic preconditioning; PO=postoperative; MINS=myocardial injury in non-cardiac surgery

high risk of cardiovascular events when undergoing an urgent major orthopaedic procedure. This could provide a possible explanation for the high rate of MINS.

We performed separate analyses to account for the different types of assays for troponin I. The analysis of high sensitive troponin I included 247 patients and the analysis of cardiac troponin I included 326 patients. We found lower point estimates in the RIPC group compared with the control group, but the interquartile ranges were wide. The lack of difference between the groups might reflect low statistical power or that an increase in troponin in MINS reflects a different pathophysiology from that in patients with myocardial infarction.

About one third of the patients had one or more missing troponin I measurements; mostly for the third or fourth postoperative measurement. Large observational studies have shown that MINS primarily occurs within postoperative day 2.[4 33] The risk of overlooking MINS because of a missing troponin I measurement should be small.

More patients in the RIPC group than control group received acetylsalicylic acid, but an unplanned analysis showed that the drug was not significantly associated with a reduced risk of MINS.

Propofol was the main agent used for intravenous sedation. In cardiac surgery and experimental studies propofol has been discussed as interfering and inhibiting the cardioprotective effects of RIPC.[34] In our trial, about 80% of the patients received intravenous propofol and we found no interaction between type of anaesthesia and RIPC. The trial was not, however, designed to draw any conclusions on this matter. The potential interaction between anaesthetic regimen and the effect of RIPC is debatable. Results from meta-analyses and clinical studies are contradictory and primarily from cardiac surgery.[29 30 35 36] To the best of our knowledge, no clinical trial has specifically investigated the influence of an anaesthetic regimen on the effect of RIPC.

Our trial design was pragmatic to ease its implementation in the clinical setting, thus the anaesthetic regimen was not standardised. The surgical procedure

and preoperative and postoperative care (for example, treatment of preoperative and postoperative pain, fluids, blood transfusions, and physiotherapy) followed national guidelines, but with local variations in each of the trial sites. The trial sites had a standardised clinical guideline for patients with hip fractures based on the Danish national guidelines.[37] The pragmatic design increases the generalisability of the trial.

The diagnosis of MINS has only recently been defined and no established international consensus on treatment exists. The management of MINS is therefore not clear.

Although we observed no local adverse effects of RIPC, the trial is too small to draw any conclusions on safety. A randomised clinical trial in cardiac surgery reported that 35 out of 801 patients (4.4%) had transient skin petechiae during RIPC, and no patients had any adverse effects with long term consequences.[30] At one year follow-up, the occurrence of clinical adverse events including death and readmission did not differ between the RIPC group and control group.[30] In vascular surgery, RIPC has been reported to reduce kidney impairment and intestinal and pulmonary injury.[38 39]

Our study was not powered to draw conclusions on the secondary outcomes, therefore the effect of RIPC on clinical outcomes needs to be replicated in a larger trial. We are currently collecting data on long term clinical outcomes and mortality.

Conclusions and future implications

In this randomised clinical trial, RIPC reduced the risk of myocardial injury within four days and myocardial infarction within 30 days of hip fracture surgery. We cannot, however, conclude that RIPC overall prevents major adverse cardiovascular events and other clinically important outcomes after surgery. Future studies should elaborate on these outcomes and the clinical cardiovascular effect of RIPC in the non-cardiac surgical setting.

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Contributors: SE, OM, and IG designed the trial and acquired and interpreted the data. CSM interpreted the data. CSM, MH, MS, PE, SK, A-MBM, OG, and JH-K acquired the data. SE drafted the first manuscript, and all authors critically revised the manuscript. All authors approved the final version of the manuscript. SE and IG are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: CSM received direct and indirect departmental research funding from Merck, Sharp & Dohme; Ferring Pharmaceuticals; and Boehringer Ingelheim outside the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the regional ethics committee of Region Zealand (No SJ-428), Denmark and the Danish Data Protection Agency (Reg-115-2014).

Data sharing: On request, an anonymised dataset will be shared provided permission is given from the Danish Data Protection Agency. The original protocol and statistical analysis plan can be obtained from the corresponding author, savb@regionsjaellan.dk, or on ClinicalTrials.gov.

The lead author (SE) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and any discrepancies from the study as originally planned and registered have been explained.

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Supplementary information: Additional tables 1-5